

Treating dyslipidaemia

—more than lipid numbers needed

Treatment for dyslipidaemia should be based on an assessment of a person's absolute risk* of suffering a cardiovascular event rather than lipid levels alone, according to *Lipid Management Guidelines – 2001*¹ released recently by the National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand.

Lipid levels need to be evaluated within the context of all factors contributing to a person's risk, such as existing coronary heart disease (CHD), diabetes mellitus, age, sex, hypertension, smoking, or a history of premature CHD in a first-degree relative. The lipid numbers alone will not adequately identify those at risk.

The factors contributing to high absolute risk of CHD as identified in *Lipid Management Guidelines – 2001* are shown in the box on the right. These have been divided into those where the evidence supporting the notion of high absolute risk is strong (e.g. systematic review or randomised controlled trials), and those where the evidence is less robust and is the result of consensus opinion based on clinical experience.

Risk assessment tools are available to calculate a person's absolute risk of CHD, taking into account all contributing factors (see page 3).

According to the guidelines, a person with a 10–15% or higher absolute risk (i.e. probability) of having a cardiovascular event in the next five years should begin a lipid-modifying program. Initially lifestyle changes are employed but pharmacological therapy will be needed for those who do not respond adequately.

Recommendations in the guidelines have been formulated without formal health-economic and cost-effectiveness analyses.

Lipid Management Guidelines – 2001 can be obtained from the Heart Foundation website at <http://www.heartfoundation.com.au>.

For details on the choice of lipid-modifying drugs and a discussion on their relative benefits and risks, doctors and pharmacists can refer to the next *NPS Prescribing Practice Review* on lipids to be mailed late February 2002. This will include the New Zealand cardiovascular risk calculator, developed by the New Zealand Guidelines Group, to help you assess absolute risk.

* See page 2 for a discussion of absolute and relative risks.

Inside ▶

Risky Business:
The difference between absolute and relative risks

Prescribing Pointers:
Lipid-modifying therapy

Modifying diet:
What effects can be expected?

Complementary update

Case studies for doctors and pharmacists

Factors contributing to high absolute risk of coronary heart disease

Based on high level evidence per National Health and Medical Research Council (NHMRC) ratings

1. Known coronary heart disease
2. Diabetes mellitus

Based on lower levels of evidence per NHMRC ratings

3. Other manifestations of atherosclerotic disease—peripheral vascular disease, ischaemic cerebrovascular disease, abdominal aortic aneurysm
4. Chronic renal failure
5. Aboriginal and Torres Strait Islander peoples
6. Familial hypercholesterolaemia
7. Familial combined hyperlipidaemia
8. An absolute risk of 10–15% or greater in the next five years according to the New Zealand cardiovascular risk calculator
9. **Either** a low-density lipoprotein cholesterol (LDL-C) > 4.0 mmol/L **or** total cholesterol > 6.0 mmol/L **plus** at least two other risk factors (high-density lipoprotein cholesterol [HDL-C] < 1.0 mmol/L, significant family history of CHD, hypertension, obesity, smoking, impaired fasting glucose or glucose intolerance, microalbuminuria or renal impairment, age ≥ 45 years)

'Lipid-modifying therapy' – what is it?

In this newsletter we have used the term 'lipid-modifying therapy' to include the following steps:

1. change diet and lifestyle
2. if initial response to diet and lifestyle changes is inadequate, combine them with drug therapy.

Risky business

The results of clinical trials are often presented in terms of *relative risk* yet many insist that such results should reflect the *absolute risk*. What is the difference and why might one be preferred over the other?

Two people buy lottery tickets, along with several million other people: the first person buys one ticket and the second buys two.

By buying two tickets, the second person has doubled the relative risk of winning. *Relative risk* compares how often a particular event occurs between two groups.

However, the *absolute risk* of winning remains very low for both individuals, being only one in several million or two in several million. Absolute risk describes the difference between how often the event occurs in the two groups, providing context to the change in risk.

How does this apply to a health example?

It is known that age contributes to the risk of CHD. How does it affect the risk of having a fatal cardiac event in the next 10 years when plasma-cholesterol concentration is lowered by 0.6 mmol/L?

From the relative risk reduction shown in the table below, it would seem that young people benefit most from reducing their plasma-cholesterol concentration by 0.6 mmol/L.

However, as the frequency of fatal cardiac events is higher in the elderly, the absolute risk reduction shows that the 80-year old man has a better chance of deriving the greatest benefit from having his plasma-cholesterol concentration reduced by 0.6 mmol/L.

The absolute risk reduction allows the number-needed-to-treat (NNT) to be calculated.* Five hundred 40-year old men need to have their cholesterol reduced by 0.6 mmol/L to prevent one fatal CHD event occurring per 10 years whereas only 23 80-year old men would need such treatment to obtain the same result.

*Guidance in calculating NNTs can be found in *Australian Prescriber* 2000;23(2):38.

	Risk of having a fatal cardiac event per 10 years			
	Baseline	After reducing plasma-cholesterol concentration by 0.6 mmol/L	Relative risk reduction	Absolute risk reduction
40-year old man	0.4%	0.2%	50%	0.2%
80-year old man	22%	17.6%	20%	4.4%

Example based on 1992 mortality rates for England and Wales

National Medicines Symposium 2002

Registrations are now open for the National Medicines Symposium 2002 – Linking people, actions and policy for Quality Use of Medicines, to be held at the National Convention Centre in Canberra, Wednesday 20 – Friday 22 March 2002.

Questions to be tackled at the Symposium include:

- How is the Quality Use of Medicines movement benefiting people in Australia?
- What is happening at the national, regional and local levels that can be of use to GPs, pharmacists, consumers, government and industry?
- What impact will current research and evaluation have on the direction of Quality Use of Medicines?

For more information or to register, please telephone Conference Solutions: 02 6285 3000; or email: nms@con-sol.com; or visit the NPS website at www.nps.org.au.

Reminder: No change to lipid-lowering drugs in 2001/02 Budget

Prior to the Budget announced in May 2001, there was some confusion regarding alleged changes to the clinical criteria for eligibility to receive subsidised lipid-modifying medications on the Pharmaceutical Benefits Scheme (PBS).

There were no changes made to either the eligibility criteria or to the range of lipid-modifying medications available on the PBS.

The Department of Health and Ageing has attempted to clarify the requirements for prescribing these drugs on the PBS by using plain English and improving the presentation in the 'yellow book'; this new format first appeared in the August 1, 2001 Schedule.



Prescribing Pointers

Lipid-modifying therapy has greatest benefits for those at greatest absolute risk of CHD

Patients with CHD (secondary prevention)

Lipid-modifying therapy is strongly recommended in patients with angina or a previous myocardial infarction (MI) to prevent future CHD events. These patients are already at high risk so there is no need to assess their absolute risk.

In the 4S,² CARE,³ and LIPID⁴ trials, patients with CHD had their absolute risk of CHD death or non-fatal MI reduced by up to 9% over five years by simvastatin or pravastatin over a wide range of plasma-cholesterol concentrations (4–8 mmol/L). A similar but less conclusive trend was achieved with the fibrate, gemfibrozil.⁵

Patients without CHD (primary prevention)

In patients without CHD, the absolute risk of a CHD event needs to be assessed. Those with a risk of 10–15% or higher over 5 years should be treated with lipid-modifying therapy.

The issue of primary prevention therapy in individuals without CHD is less straightforward. The evidence from the principal primary prevention trials—WOSCOPS,⁶ AFCAPS/TexCAPS,⁷ and the Helsinki Heart Study⁸—is not as persuasive as that from the secondary prevention trials.

For example, the WOSCOPS population had risk factors that probably showed primary prevention in a good light: men were recruited from a population with one of the highest incidences of ischaemic heart disease in the world; their plasma-cholesterol levels were in the highest quartile found in the British population; up to one-sixth of the participants were not necessarily asymptomatic as they had established angina or ECG abnormalities; and 44% were current smokers.

Additionally, these trials have not shown any difference in overall mortality between those taking lipid-modifying drugs and those who were not.

A comparison of primary and secondary prevention studies highlights that those at greatest risk derive the greatest benefits: study results indicate that approximately three times as many people without CHD need to be treated for five years to prevent one CHD event than people with CHD.⁹

Certain groups (such as women, people aged 75 years and older, and people with diabetes) have been generally under-represented in the published trials to date. Studies designed specifically to investigate the effects of lipid-modifying drugs in these groups are yet to be reported.

Similarly, the evidence regarding the effects of statins on stroke is unclear despite the positive conclusions arrived at.¹⁰ It appears from study results that greater effects are seen in preventing stroke in patients with CHD than in those without CHD. As trials to date have not generally included patients with existing cerebrovascular disease, further evidence is needed before firm conclusions can be made on lipid-modifying therapy and stroke.

Assessing a patient's risk

It is not always cost-effective for the community if all patients who might benefit from therapy are considered eligible to receive that therapy. A more realistic approach is to agree on a level of risk at which treatment should be offered and then to identify individuals who exceed that level of risk.¹¹ Consistent with international CHD risk estimations, *Lipid Management Guidelines – 2001* proposes that the level of risk be 10–15% or greater over 5 years.

Risk can be assessed by either using one of the available risk assessment tools (e.g. the New Zealand cardiovascular risk calculator, developed by the New Zealand Guidelines Group) or by counting risk factors.¹ These risk assessment tools are based on observational studies (predominantly the Framingham population) where certain variable factors regarded as disease predictors are weighted to enable the overall risk to be estimated; the factors include age, sex, smoking status, diabetes mellitus, and blood pressure. Although this approach has not been validated to improve coronary outcomes, the tools attempt to make risk assessment possible in the primary care setting.

Calculating the level of risk should take into account modifiable risk factors. For example, a risk of 10.1% in a smoker should lead to advice to stop smoking initially rather than immediate drug therapy. Indeed, initial management should attempt to redress any modifiable risk factors: diet, the level of physical activity, stopping smoking, and reducing excess alcohol intake.

In conclusion

Some of the answers to the uncertainties discussed above may evolve from the largest trial assessing cardiovascular outcomes with lipid-modifying therapy. The UK-based Heart Protection Study, conducted in 20,000 patients, investigated the effects of simvastatin and various antioxidant vitamins on cardiovascular outcomes in those with and without heart disease. Simvastatin was reported to show significant benefits in total mortality and major cardiovascular events such as MI, stroke, and other vascular complications. Results can be more rigorously appraised once this study is fully published.



What does the research say?

Modifying diet—what effects can be expected?

- Metabolic studies of short duration show that reductions in plasma cholesterol can appear within just a few weeks of modifying diet
- Dietary interventions can reduce total cholesterol by 15% when they are adhered to
- In clinical trials of lipid-modifying drugs, dietary modifications and supportive advice were maintained throughout the study period, underpinning the effects seen with drug therapy
- Modifications in diet, physical activity and other aspects of lifestyle reduce absolute cardiovascular risk over and above the improvement they provide to the lipid profile

A meta-analysis¹ found that by replacing 10% of dietary calories obtained from saturated fats with isocaloric amounts of polyunsaturated (5%) and monounsaturated (5%) fats, the total cholesterol concentration was reduced by about 0.6 mmol/L, achieved predominantly through reductions in LDL-C. When daily cholesterol intake was approximately halved in addition to the substitution of unsaturated fats, the reduction in total cholesterol was about 0.8 mmol/L, representing a 10–15% reduction.

The Lyon Diet Heart Study² has shown that a Mediterranean-style diet (high in fresh fruits and vegetables, fish, poultry, cereal grains, nuts) can significantly reduce cardiac deaths and non-fatal

MIs (from 4.1% down to 1.2%) when used in addition to standard post-MI drug therapy. Interestingly, the reduced incidence in cardiac events was seen without there being any significant difference in the lipid profile between the diet and control groups.

The Lyon study also demonstrates that adopting and complying with new dietary habits is an achievable goal as the results were obtained over a period of 46 months.

A Cochrane review of reduced or modified dietary fat interventions³ highlighted that the largest reduction in cardiovascular events was seen in trials where the participants were involved for more than two years.

New “non-prescription” pad tackles healthy eating

NPS has prepared another “non-prescription” pad in the series, this time designed to assist doctors “prescribe” appropriate lifestyle changes for patients with dyslipidaemia.

As with other pads in the series, tear-off “scripts” are included that the doctor can use as the basis for discussion with the patient. The scripts in this pad include practical suggestions for dietary changes, prepared with assistance from the Heart Foundation, that can be tailored to suit each patient’s needs. Information is also provided to assist doctors “prescribe” other lifestyle changes to reduce cardiovascular risk factors.

Pads will be available free of charge from the NPS at the end of February 2002. An order form will be included in the next issue of the *NPS Prescribing Practice Review* to be mailed to all GPs in late February.



The new pad “prescribing” dietary and lifestyle changes for managing dyslipidaemia is the next in our series that includes the popular Symptomatic Management Pad for Acute URTIs and Acute Bronchitis, 40,000 of which have been distributed in Arabic, Chinese, English, Greek, Italian and Vietnamese.



A Complementary Update:

There are many complementary products available over-the-counter to people concerned about their 'cholesterol'.

Policosanol

(Blackmores Policosanol)

Policosanol, derived from sugar cane, has become available recently. Randomised, controlled trials evaluating policosanol in the treatment of hypercholesterolaemia have found a dose-dependent effect on the lipid profile: 5 mg/day reduced total cholesterol by 12%, LDL-C by 16% and increased HDL-C by 5%, while 10 mg/day reduced total cholesterol by 18%, LDL-C by up to 28% and increased HDL-C by up to 29%. These trials were generally of short duration with low patient numbers.

The most frequent adverse effects associated with policosanol are weight loss, polyuria, headache, dizziness and polyphagia. Policosanol also inhibits platelet aggregation which may increase the risk of bleeding in patients taking aspirin concomitantly.

At best, the effects of policosanol on the serum lipoprotein profile appear to be comparable to a low-dose statin or a 2–3 g daily intake of plant sterols. The majority of the studies used a 10-mg dose so a month's supply will cost the patient around \$90–\$100.

Patients expressing interest in policosanol should be advised that, according to current evidence, any specific effect is small and improvement in cardiovascular outcomes has not been demonstrated. Therefore, policosanol has a limited role in the management of patients with dyslipidaemia, especially those with established cardiovascular disease.

Fish oils

(e.g. BiOmega-3, Efamarine, Fishaphos, Himega, Maxepa)

Fish and fish oils act to decrease triglyceride levels. Clinical trials using supplements of the active constituent of fish oils, omega-3 polyunsaturated fatty acids (omega-3 PUFA), found they moderately reduced cardiovascular morbidity and mortality in people who had already had an MI.^{1,2} Supporting these results, the Lyon Diet Heart Study noted an improved prognosis in those consuming higher proportions of foods containing omega-3 PUFA. Patients in the above studies also received standard post-MI pharmacological management including aspirin, beta-blockers, statins and ACE inhibitors.

Consuming a fish-based meal at least twice a week is encouraged. If fish oil supplements are used, a daily dose of at least 2 g omega-3 PUFA is recommended;³ the content of omega-3 fatty acids varies so the dosage must be calculated for each product.³

Plant sterols⁴

(e.g. Flora pro-activ, Lo-cholesterol, Logicol)

Plant sterols and stanols have a similar structure to cholesterol. When added to the diet (notably as margarine) they reduce the amount of dietary and biliary cholesterol absorbed.

Studies with sterol-enriched foods have shown that about 2 g of plant sterols and stanols reduces LDL-C by 10–15%; this effect is additive to reductions achieved through either dietary changes in fatty acid consumption or statins.

No adverse effects were reported in clinical trials but long-term safety studies have not been conducted. Plant sterols can reduce the gut absorption of carotenoids; it is for this reason that their use is not recommended in children or during pregnancy. Patients using these spreads should be encouraged to consume more yellow and orange vegetables and fruits.

Plant sterols provide an additional option for lowering plasma cholesterol, although any benefits in terms of reducing heart disease by lowering cholesterol in this way remain to be demonstrated. A daily intake of 2–3 g (1–1½ tablespoons of plant sterol-enriched margarine or 3–4 slices of bread thinly spread with this margarine) is recommended.

Other

Vitamin E: Recent, large-scale, outcome trials^{1,5} have failed to detect any beneficial effects of vitamin E in reducing CHD events or mortality.

Garlic: There is insufficient evidence to recommend garlic supplements to protect against cardiovascular disease.

Lecithin: There is no strong evidence that lecithin acts as a cholesterol-lowering agent.



Health professionals, do you need information on therapeutic drugs?

Contact the NPS Therapeutic Advice and Information Service

Phone 1300 138 677

Consumers targeted in national campaign

New resources produced by the Heart Foundation will assist GPs to provide their patients with up to date, evidence based information on dietary and other lifestyle changes for lipid management. The fridge magnet and brochure targeted to consumers have been produced as part of a campaign being conducted by the Heart Foundation in consultation with Consumers' Health Forum and other consumer groups, and funded under a grant from the Commonwealth Department of Health and Ageing.

Information provided to consumers will include key healthy eating messages to lower blood lipids, as well as information about other lifestyle changes and the role of medication and complementary medicines.

The fridge magnet and brochure will be available free of charge to consumers by the end of March. GPs can refer patients who need this information to the Heart Foundation's Heartline on 1300 36 27 87. GPs can also obtain samples by contacting Heartline.

What's What

HMG-CoA reductase inhibitors ('statins')	
Atorvastatin	Lipitor®
Fluvastatin	Lescol®, Vastin®
Pravastatin	Pravachol®
Simvastatin	Lipex®, Zocor®
Fibrates	
Gemfibrozil	Ausgem®, Gemhexal®, Jezil®, Lipazil®, Lopid®
Other	
Cholestyramine	Questran Lite®
Colestipol	Colestid®
Nicotinic acid	Available as generic only

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More than lipid numbers needed

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The information contained in this material is derived from a critical analysis of a wide range of authoritative evidence. Any treatment decisions based on this information should be made in the context of the individual clinical circumstances of each patient.



National Prescribing Service Limited

Our goal To improve health outcomes for Australians through prescribing that is: ▲ safe ▲ effective ▲ cost-effective
Our programs To enable prescribers to make the best prescribing decisions for their patients, the NPS provides:
▲ information ▲ education ▲ support ▲ resources

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